FIG. 1—Principles of surgical ward design.

types of staphylococci have become established in hospital wards without obvious changes in environmental conditions and a two-year study is insufficient for final assessment. Nevertheless, we are convinced that the provisions in the new unit contributed significantly to the reduction in serious hospital infection.

The principles of ward design adhered to are brought

together in Fig. 1; all relate to control of hospital cross-infection. At a conference on this subject held some years ago Sir James Howie stated that there were no quick and facile answers to the problem and that administrative authorities might have to be prepared to make some expensive mistakes. This meant, he said, that new hospital accommodation might have to be built, with a still incomplete appreciation of all the factors involved in infection control (Conference Report, 1961). The new surgical unit in Aberdeen has been expensive, but, taking all results into account, perhaps not a mistake.

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We also wish to thank Mr. John Brand for considerable technical help.

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A Within-patient Comparison of Debrisoquine and Methyldopa in Hypertension

A. HEFFERNAN, A. CARTY, K. O'MALLEY, J. BUGLER

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Summary

In a titrated dose cross-over trial of debrisoquine and methyldopa in 38 hypertensive patients neither drug was superior in lowering supine or standing diastolic pressure with a minimum of side effects. Methyldopa caused significantly greater reduction of supine ($P < 0.001$) and standing ($P < 0.02$) systolic pressure but caused intolerable side effects in two patients. Tiredness was the most characteristic and troublesome side effect with methyldopa and postural hypotension was prominent in patients while on debrisoquine.

Introduction

Our initial studies with debrisoquine showed that it is an effective antihypertensive agent with a relatively low incidence of side effects (Heffernan and Carty, 1970). To date no formal comparative clinical trial between debrisoquine and other sympathetic blocking agents has been carried out. A within-patient comparison of debrisoquine and methyldopa with some modifications was designed along the lines established by Prichard, Johnston, Hill, and Rosenheim (1968).

Patients and Methods

Each patient had a "run-in" period on each drug during which the dosage was increased to give the desired reduction of blood pressure with no or with tolerable side effects. There followed a three-month period of assessment before the patient changed to the other drug. The order of administration of the two drugs under trial was randomized. The commercially available tablets of debrisoquine 10 mg and methyldopa 250 mg were used in a three times daily routine. Hydrochlorothiazide with potassium was added if blood pressure control was not satisfactory with the primary drug alone. At the end of each period of assessment patients were questioned directly about specific side effects, but those side effects complained of spontaneously by patients at intermediate visits were also recorded.

At the beginning of the trial a range of standing diastolic pressure was chosen which would be regarded as satisfactory control for each patient. For most of our patients the range 90-99 mm Hg was selected, but a target of 80-89 mm Hg was set for those with uncomplicated hypertension who were under 45 years old. Levels not more than 10 mm Hg above the chosen range were regarded as fair control, but inability to maintain even fair control or the occurrence of intolerable side effects was regarded as a failure of treatment.

Blood pressure was measured by one of us (A.C., K.O.M., or J.B.) on the London School of Hygiene and Tropical Medicine sphygmomanometer (Rose, Holland, and Crowley, 1964). Pressure was measured one minute and three minutes after lying down and one minute after standing up. Only the three-minute supine and the standing pressures were analysed. These physicians had no record of previous readings or of the drug being taken by the patient at the time. The physician (A.H.) who supervised the clinical care of the patients and adjusted dosage had all this information.

Mater Misericordiae Hospital, Dublin

- A. HEFFERNAN, M.D., M.Sc., Lecturer in Medicine (Present address: St. Vincent's Hospital, Dublin)
 A. CARTY, M.B., M.R.C.P.I., Medical Tutor
 K. O'MALLEY, M.D., M.R.C.P.I., Registrar (Present address: Department of Therapeutics, University of Dundee)
 J. BUGLER, M.B., B.Ch., Registrar

TABLE I—Details of Patients and Average Blood Pressure from Periods of Assessment (Seven Two-weekly Visits over 12 Weeks for Each Drug)

Case No.	Sex and Age	Type of B.P.	Pre-treatment Standing (mm Hg)	Start of Trial				Debrisoquine				Methyldopa			
				Fundus	E.C.G. L.V.	Urea (mg/100ml)	Standing B.P. (mm Hg)	Blood Pressure (mm Hg)		mg/day	Hydrochlorothiazide K	Blood Pressure (mm Hg)		mg/day	Hydrochlorothiazide K
								Supine	Standing			Supine	Standing		
1	M.54	E.	199/117	II	+	38	199/117*	183/106	170/99	60	—	166/97	148/89	1,750	+
2	M.40	E.	160/100	II	—	23	139/94	130/76	129/82	20	—	120/71	119/78	750	—
3	F.61	E.	220/140	II	—	37	186/108	181/105	163/91	50	—	154/92	138/90	1,500	—
4	F.59	E.	200/140	II	—	42	146/107	173/92	162/93	60	—	171/97	155/96	2,250	—
5	F.58	E.	215/120	II	+	37	209/111	175/93	150/91	57.5†	—	165/93	152/92	1,500	—
6	F.60	E.	240/140	III	+	56	171/87	203/104	183/100	120	—	169/99	153/98	3,000	+
7	F.51	R.	200/105	II	—	35	200/125	145/90	125/87	20	+	150/96	146/98	2,250	+
8	M.51	E.	200/120	II	+	35	178/98	208/86	182/83	90	—	188/83	171/88	2,250	—
9	M.55	E.	240/130	II	—	37	134/93	165/96	127/88	60	—	155/95	138/91	3,000	—
10	M.53	E.	280/120	II	—	25	166/97	167/83	142/79	40	—	141/85	137/92	1,500	—
11	F.46	E.	210/125	II	—	49	156/87	155/91	155/96	20	+	156/80	144/83	1,750	—
12	M.62	E.	230/130	II	—	40	192/114	177/101	158/98	60	—	143/85	151/93	3,000	+
13	F.65	R.	230/130	II	—	30	152/82	179/91	167/87	30	—	158/84	137/80	1,500	—
14	M.50	E.	170/120	II	—	44	108/67	151/84	130/83	20	—	152/89	134/92	500	—
15	F.56	E.	210/130	II	—	37	190/104	177/93	147/85	49.1†	—	152/82	145/89	2,250	—
16	M.67	R.	180/110	II	—	47	212/123	173/100	165/94	60	—	160/95	141/93	1,041§	—
17	M.18	R.	190/140	II	—	56	175/100	147/92	126/89	70	+	149/95	143/96	1,000	+
18	F.63	R.	210/120	II	—	52	154/98	186/91	167/87	30	—	165/95	144/95	1,500	—
19	F.61	R.	180/115	II	—	44	125/85	155/92	148/90	40	—	141/90	140/94	1,000	+
20	M.66	E.	210/130	II	—	36	173/114*	154/102	149/98	40	—	157/103	151/99	1,000	—
21	F.64	R.	250/130	II	—	31	170/100	161/96	141/98	50	+	148/91	136/94	2,250	+
22	F.42	R.	190/140	II	—	43	156/98	174/94	160/97	30	—	146/90	146/96	750	—
23	F.68	E.	180/120	II	+	30	160/103	124/85	122/87	30	+	136/89	128/88	1,500	+
24	F.45	E.	200/130	II	—	36	208/100	157/94	152/94	29.1†	+	—	—	—	—
25	F.61	E.	200/115	II	—	23	182/96	163/86	162/89	20	—	153/84	153/88	500	—
26	F.65	E.	230/140	II	+	42	145/92	158/97	140/88	20	—	149/94	137/92	1,500	—
27	M.60	E.	195/120	II	—	33	189/112	170/95	167/96	30	—	153/84	150/89	1,000	+
28	F.55	E.	210/120	II	—	21	195/88	181/90	164/89	60	—	162/95	139/88	3,000	+
29	F.48	E.	170/114	II	—	43	170/114*	168/92	162/86	60	—	149/85	150/93	3,000	+
30	M.44	C.A.	200/120	II	+	29	137/93	165/89	147/96	41.6†	—	159/90	143/94	1,500	+
31	F.64	E.	235/115	II	—	27	218/106	189/91	189/96	50	—	166/83	166/88	1,500	+
32	M.63	E.	230/120	II	+	33	174/111	162/92	156/94	40	—	163/90	161/93	2,000	—
33	F.41	E.	200/120	II	—	33	188/131*	158/106	144/99	60	+	135/92	119/89	2,250	+
34	F.62	E.	215/140	II	+	27	195/106	173/100	161/97	50†	—	142/92	144/93	2,250	+
35	F.56	E.	250/120	II	—	42	165/105	214/99	187/94	40	—	—	—	—	—
36	F.59	E.	210/130	II	—	47	161/90	156/93	152/95	30	—	156/93	145/94	1,000	—
37	F.59	E.	180/121	II	—	26	180/121*	155/95	147/94	30	+	156/93	155/95	750	—
38	F.43	E.	210/130	II	—	43	202/138	189/116	168/111	70	+	174/112	169/112	3,000	+

E. = Essential. R. = Renal. C.A. = Coarctation of aorta. L.V. = Left Ventricle. *Not on treatment.

†Debrisoquine dose decreased. §Methyldopa dose decreased. ‡Diuretic discontinued.

The clinical details of the 38 patients who completed the trial are given in Table I. During the trial these patients attended as outpatients and were able to go about their normal daily activities. Three other patients were withdrawn from the trial—one left the district, one had a myocardial infarct, and the third, who had advanced valvular heart disease, developed cardiac failure. All except 5 of the 38 patients had received at least one antihypertensive drug before the trial—7 debrisoquine, 25 methyldopa, 9 guanethidine, 5 bethanidine, and 8 diuretics. No patient received tricyclic antidepressant drugs during the trial (Skinner, Coull, and Johnston, 1969).

Results

DOSAGE

The average daily dose of each drug required by each patient is shown in Table I. The dose of debrisoquine was decreased by 10 mg because of postural hypotension in four patients and of nightmares in one patient. Methyldopa was decreased by 500 mg in one patient because of postural hypotension. The mean of the average daily dose used in the period of assessment was debrisoquine 46 mg (S.D. 21.2 mg) and methyldopa 1,716 mg (S.D. 780.8 mg).

Ten patients while receiving debrisoquine and 15 while on methyldopa required hydrochlorothiazide K. This had to be discontinued because of postural hypotension in one patient on debrisoquine and in one on methyldopa. Another patient on methyldopa had diuretic discontinued because of gout (Table I).

LEVELS OF CONTROL

The average levels of blood pressure attained by each patient during the period of assessment on each drug are shown in

Table I. Thirty-one patients achieved satisfactory levels of control on both drugs—that is, the average standing diastolic pressure during the period of assessment was within the level aimed at in planning the trial. Two patients who had satisfactory control on methyldopa had only fair control on debrisoquine, while one patient who was in the satisfactory range on debrisoquine was only in the fair range on methyldopa. Another patient had only fair control on both drugs.

One patient satisfactorily controlled on debrisoquine was unable to proceed with the trial on methyldopa because of extreme tiredness. Another patient with fair control on debrisoquine as the dose had been decreased because of nightmares was unable to tolerate methyldopa because of severe tiredness and terrifying nightmares. Treatment failed in one patient with both drugs, primarily because of poor control, despite debrisoquine 70 mg and methyldopa 3,000 mg together with hydrochlorothiazide K 100 mg with each drug. Any further increase in debrisoquine brought on definite symptoms of postural hypotension, and higher doses of methyldopa caused unwanted drowsiness. Nevertheless, 37 of the 38 patients on debrisoquine and 35 of the 36 who could tolerate methyldopa had an average standing diastolic pressure at the end of the period of assessment of 100 mm Hg or less, this being the level most usually accepted as good control.

No statistical difference was found between the mean of the average diastolic supine and standing pressures for the 38 patients on debrisoquine and the 36 who completed the trial on methyldopa; supine diastolic on debrisoquine 94 mm Hg (S.D. 7.90 mm Hg) and on methyldopa 91 mm Hg (S.D. 7.59 mm Hg); standing diastolic on debrisoquine 92 mm Hg (S.D. 8.20 mm Hg) and on methyldopa 92 mm Hg (S.D. 5.85 mm Hg).

Methyldopa caused a significant lowering of the mean of the average systolic supine ($P < 0.001$) and standing ($P < 0.02$) pressure in comparison with debrisoquine in the patients who completed the period of assessment on both drugs: supine

systolic on debrisoquine 168 mm Hg (S.D. 18.43 mm Hg) and on methyldopa 154 mm Hg (S.D. 12.41 mm Hg); standing systolic on debrisoquine 154 mm Hg (S.D. 17.39 mm Hg) and on methyldopa 145 mm Hg (S.D. 11.81 mm Hg).

There are two obvious factors that might have contributed to this. Firstly, the order of administration was analysed but no effect on blood pressure control was found. Secondly, the addition of diuretic to the primary drug was considered. The means of the average supine (161 mm Hg, S.D. 23.04 mm Hg) and standing (149 mm Hg, S.D. 19.20 mm Hg) systolic pressures for the nine patients who received diuretic with debrisoquine throughout the period of assessment were not significantly different from the means of the average supine (150 mm Hg, S.D. 12.44 mm Hg) and standing (146 mm Hg, S.D. 13.54 mm Hg) systolic pressures of the 13 patients receiving methyldopa and diuretic. Furthermore, the dose of diuretic received by both groups was not significantly different. When, however, the means of the average supine (171 mm Hg, S.D. 16.12 mm Hg) and standing (157 mm Hg, S.D. 15.61 mm Hg) systolic pressures of the 28 patients receiving debrisoquine without diuretic are compared with the supine (156 mm Hg, S.D. 12.63 mm Hg) and standing (145 mm Hg, S.D. 10.91 mm Hg) systolic blood pressures of the 21 patients receiving methyldopa without diuretic, the same result as for the group as a whole is obtained—that is, the supine ($P<0.005$) and standing ($P<0.005$) systolic pressure is significantly lower in the patients while receiving methyldopa.

ORTHOSTATIC HYPOTENSION

To show a difference in orthostatic hypotension in patients while on debrisoquine in comparison with methyldopa only those whose average standing diastolic pressures were in the range 80 to 100 mm Hg with no more than 10 mm Hg between them were chosen. These criteria were satisfied in 30 patients. The orthostatic hypotension was measured as the difference between the average mean supine and standing blood pressure. Mean blood pressure equals diastolic plus one-third of pulse pressure. The greater orthostatic effect of debrisoquine in comparison with methyldopa, which by signed-ranks analysis was significant ($0.01>P>0.001$), is clearly shown in the chart. Further analysis by the Mann-

Comparison of the orthostatic hypotension produced by debrisoquine and methyldopa.

Whitney test showed that the addition of hydrochlorothiazide K to the primary drug was not a significant factor in producing the greater orthostatic effect of debrisoquine.

Signed-ranks analysis of the ratios of the reduction of the level in the supine blood pressure to the reduction of that standing produced by each drug in each patient shows that for a given reduction of blood pressure in the standing position methyldopa produces relatively more reduction in the level in the supine position than debrisoquine ($0.02>P>0.01$).

SIDE EFFECTS

The side effects recorded were classified as major if they were severe, extremely unpleasant, or necessitated a decrease in dosage (Table II); all others were considered minor. It was often difficult to decide whether a complaint for which no other reason could be found should be classified as a minor side effect. If it was persistent—that is, reported on more than one visit to the clinic—then it was classified as a minor side effect. Statistical analysis of the major and minor side effects showed no significant difference in the incidence of side effects occurring with either debrisoquine or methyldopa; the presence or absence of side effects ($\chi^2=0.075$; $0.80>P>0.70$); a more detailed analysis of major and minor side effects ($0.90>P>0.80$); and of the minor side effects only ($\chi^2=0.008$; $0.95>P>0.90$).

At the end of the trial patients were asked to place in order of preference the drugs they had received. Twelve preferred debrisoquine; the main reason in 10 was that they had more energy and felt less tired than when receiving methyldopa. Seven of the nine who preferred methyldopa did so because they feared the hypotensive episodes which occurred with debrisoquine. These reasons follow the pattern as seen with the side effects (Table II).

TABLE II—Side Effects

	Debrisoquine (38 Patients)	Methyldopa (36 Patients)
<i>Major Side Effects</i>		
Hypotension on rising, during day, or after exercise requiring change of dose	6	2
Tiredness	0	1
Diarrhoea	0	2
Nightmares	1	0
Failure of ejaculation	1	0
<i>Minor Side Effects*</i>		
Dizziness on rising, during day, or after exercise not requiring change of dose	8	3
Tiredness	7	8
Disturbance of bowel action	9	7
Headache	9	3
Nasal obstruction	2	5
Dry mouth	2	4
Unpleasant taste	2	1
Sore tongue	1	0
Nausea	1	0
Heartburn	1	0
Epigastric discomfort	0	2
Nocturia	4	1
Dreams	0	1

*Several patients had more than one minor side effect.

The presence or absence of side effects is not significantly affected by the order of administration of the drugs ($\chi^2=0.962$; $0.50>P>0.30$). Major side effects appeared more prominent but not statistically so on the second drug ($\chi^2=2.498$; $0.20>P>0.10$). Also two patients could not tolerate the second drug. Nevertheless, 17 patients showed a pronounced preference for the second drug. There is no significant difference in the incidence ($\chi^2=0.067$; $0.80>P>0.70$) or quality ($\chi^2=0.80$; $0.80>P>0.70$) of side effects occurring with either drug when patients achieving similar levels of blood pressure control are compared. The presence or absence of diuretic does not seem to affect this comparison of the incidence or quality of the side effects.

CLINICAL CONDITION

All patients who completed both phases of the trial remained equally well on both drugs and there was no striking change in serum electrolytes, urine analysis, or E.C.G. The mean blood urea for the patients on debrisoquine was 43.60 mg/100 ml (S.D. 16.61 mg/100 ml) and on methyldopa 40.36 mg/100 ml (S.D. 13.66 mg/100 ml). This difference is not significant ($0.40>P>0.30$). Full blood count showed no change, except that in one patient the total white cell count

fell from 3,900 before treatment to 2,600/mm³ while on methyl-dopa with a drop in neutrophils from 61 to 54% and a relative increase in lymphocytes from 35 to 42%. While on debrisoquine the white cell count increased to 8,100/mm³ and 65% of this was neutrophils and 30% lymphocytes. Further study of this patient is necessary to decide if this is a toxic effect of methyl-dopa.

Discussion

In this trial of debrisoquine and methyl-dopa in the treatment of patients with moderately severe hypertension, neither drug showed a superior ability to lower the supine and standing diastolic blood pressure with a minimum of side effects. Methyl-dopa, however, produced a significant reduction in both the supine and the standing systolic blood pressure which was not influenced by the diuretic supplement.

Side effects which are inevitable with all the sympathetic blocking agents can be a reason for patients defaulting. Of the 38 patients, two were unable to tolerate methyl-dopa because of side effects. This intolerance of side effects with methyl-dopa has been noted previously in up to 20% of patients (Prichard *et al.*, 1968).

It is very difficult to compare side effects, and to facilitate this they were classified as major or minor. No significant difference in the incidence of the major and minor side effects with either drug was found in those who completed both phases of the trial, though the type of side effect varied with each drug. This also came out in the patient's reasons for preferring one drug to the other, but no clue was apparent from which a patient's choice of drug could have been deduced in advance. Tiredness was the most characteristic side effect with methyl-dopa, patients often not realizing how tired they were until they changed drugs. Postural and exer-

cise hypotension were more prominent with debrisoquine though they were easily controlled by a small adjustment in dosage. This prominence of different side effects with one sympathetic blocking agent more than another is a manifestation of their slightly different pharmacological actions at the cellular level. Detailed statistical analysis confirmed that debrisoquine produced greater orthostatic hypotension than methyl-dopa, and this was not influenced by the addition of hydrochlorothiazide K (see Chart). This latter finding is surprising because of our previous impression (Heffernan and Carty, 1970) and that of Gent and Bacon (1967) that the postural effect of debrisoquine is potentiated by diuretics.

Another reason not often considered why patients who require long-term drug treatment for any disease default is the expense of the drugs. The cost of the average daily dose of debrisoquine used in this trial is about one-third that of methyl-dopa.

We are grateful to Professor T. B. Counihan for allowing us to study patients under his care and for his continuing interest in the trial. Dr. D. L. Scott, of Roche Products Ltd., and Dr. M. F. Grayson, of Merck Sharp & Dohme, deserve our thanks for helping in the design of the trial, for supplying the tablets, and for always being available to discuss problems and progress. Professor G. J. Bourke, of the department of social and preventive medicine, University College, Dublin, and Mr. K. Wilson, of the Economic and Social Research Institute, Dublin, gave invaluable help in the statistical analysis for which we are grateful.

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Lipoprotein Electrophoretic Patterns, Serum Lipids, and Coronary Heart Disease

J. R. MASAREI, MARGARET SUMMERS, D. H. CURNOW, K. J. CULLEN,
M. G. McCALL, N. S. STENHOUSE, T. A. WELBORN

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Summary

Lipoprotein electrophoresis was performed on serum from subjects with and without coronary heart disease, and the patterns compared with the serum concentrations of triglyceride and cholesterol. The beta- and pre-beta-lipoproteins, expressed as a percentage of the total lipoprotein, correlate strongly with

the cholesterol and triglyceride concentrations, respectively. The beta- and pre-beta-lipoprotein concentrations are even more strongly correlated with these lipid measurements. The lipoprotein pattern does not have greater discriminant value for coronary heart disease than does the triglyceride or cholesterol concentration. There would seem to be little justification for the use of lipoprotein electrophoresis in screening the general population for coronary heart disease.

Introduction

Following the 1966 Busselton community health survey (Curnow *et al.*, 1969) a follow-up study was made in July 1968 of a group of subjects with a survey diagnosis of "probable" or "possible" coronary heart disease together with a group of controls. The aspect of the study reported here concerned the proposition that lipoprotein patterns might prove to be a valuable index of the presence of coronary heart disease, thus adding to the power of biochemical determinations to locate subjects at risk of this disease.

Royal Perth Hospital, Western Australia

J. R. MASAREI, M.D., M.C.P.A., Registrar in Biochemistry
MARGARET SUMMERS, B.Sc., Chemist, Department of Biochemistry

University of Western Australia

D. H. CURNOW, PH.D., F.R.A.C.I., Professor of Clinical Biochemistry
M. G. McCALL, D.PHIL., M.R.A.C.P., Senior Lecturer in Medicine
N. S. STENHOUSE, M.Sc., Director of Raine Medical Statistics Unit
T. A. WELBORN, M.B., M.R.C.P., Raine Research Fellow

Georgiana Molloy Centre, Busselton, Western Australia

K. J. CULLEN, M.D., M.R.C.P.E.D., General Practitioner